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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,000	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,11-14,16-22,24-26,28-31,34-36 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9,11-14,16-22,24-26,28-31,34-36 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 4, 33 and 40 have been canceled. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain pending and are under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 6-16-04 have been fully considered but they are not persuasive.

Applicants are reminded that the response should begin with support for the amendments followed by arguments regarding each rejection.

Claim Objections

The phrase "inserting an injector selected from the group consisting of a syringe needle and catheter" in claim 1 can be stated more clearly as "inserting a needle or catheter".

In claim 1, step a) the phrase "inserting an injector... ...into a an artery in said limb" has "a" and "an" together.

In claim 1, step a) the phrase "inserting an injector... ...into an artery in said limb" should be "inserting an injector... ...into an artery in a limb of a mammal" to be more clear and to parallel the language in the preamble.

In claim 1, steps b) and c) are unclear. Step c) limits how the device in step b) is applied. Applying pressure using the device in step c) is not really a separate step. It limits the function of the cuff in step b). Simplify the steps into

one step, e.g. applying a device to the skin of said limb such that blood flow to the limb is occluded.

Use of the term "impeding" (step b) and "occluding" (step c) together in claim 1 is confusing.

In claim 35, delete "surrounding said limb" to be more clear.

The phrase "inserting an injector selected from the group consisting of a syringe needle and catheter" in claim 39 can be stated more clearly as "inserting a needle or catheter".

In claim 39, step a) the phrase "inserting an injector... ...into a blood vessel in said limb in the mammal" should be "inserting an injector... ...into an artery in a limb of a mammal" to be more clear and to parallel the language in the preamble.

The phrase "applying pressure..." in claim 39, step a) is a separate step and should be step b). this phrase can also be simplified, e.g. --applying a device to the skin of said limb such that blood flow through the blood vessel is occluded--.

The phrase labeled "c) wherein function..." in claim 39 is not a step. The phrase is describing a functional limitation of the steps and does not require an active step.

Claim Rejections - 35 USC ' 112

I. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The rejection regarding "an injector" (claims 1, 39) has been withdrawn in view of the amendment.

The new phrase "syringe needle" in claim 1 and 39 does not have support on pg 31, which only teaches a needle, or on pg 23 or 25, which only describes a catheter.

The phrase "impeding blood flow to the surface of the skin" in claims 1 and 39 does not have support in the specification as originally filed and is new matter.

The phrase "sufficient pressure" in claim 1 does not have support in the specification as originally filed.

Enablement

The rejection regarding delivering a polynucleotide to the specific muscle cells in claims 6-9, 11-14, 16-22, 24-26, 28, 31 and 34-36 has been withdrawn because the claims are limited to injecting a limb with a polynucleotide and delivering the polynucleotide to skeletal muscle cells of the same limb. Example 10 taught injecting the upper portion of a rat leg with a plasmid and obtaining delivery of the plasmid to a foot skeletal muscle in the rat leg. Example 1 on pg 23 teaches injecting plasmid into the arm or leg of a monkey by inserting a catheter into the brachial artery of the arm or the political artery of the leg, and cuffing the arm or leg proximal to the injection site (closer to the trunk). Example

3 on pg 25-28 shows the skeletal muscle cells distal to the site of injection showed luciferase expression – an indication that the plasmid was delivered to the skeletal muscle cells of the limb injected distal to the site of injection.

II. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a protein operably linked to a promoter and wherein said protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for 1) injecting the polynucleotide to the limb proximally to the applied pressure and obtaining delivery of the polynucleotide to the skeletal muscle cells of the limb distally to the applied pressure; 2) expressing a polynucleotide in skeletal muscle cells by injecting a viral vector into a blood vessel of a limb and applying a cuff proximal to the site of injecting; or 3) administering any polynucleotide as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 requires inserting an injector into an artery in a limb of a mammal, applying a device to the skin of the limb, applying pressure to the limb with the device and injecting a solution containing "polynucleotides through the injector into the lumen of said artery distal to the occlusion thereby delivering the

polynucleotides to said skeletal muscle cells distal to said occlusion." Claim 1 encompasses inserting the injector to the limb proximally to the applied pressure and injecting the polynucleotides distally to the applied pressure. I.e. claim 1 is not limited to inserting the injector distally to the applied pressure.

Claim 3 encompasses injecting a viral vector into a blood vessel of a limb to obtain delivery to a skeletal muscle cell.

Claims 6-9, 11-14, 16-22, 24-26, 28, 31 and 34-36 require delivery to specific muscles within the limbs.

Claim 39 requires inserting an injector into a limb blood vessel of a mammal, applying pressure using a device external to mammalian skin, "injecting a solution of the polynucleotides into the lumen of the vessel distal to the occlusion", and maintaining function of the limb. As such, claim 39 also encompasses inserting the injector to the limb proximally to the applied pressure and injecting the polynucleotides distally to the applied pressure. I.e. claim 39 is not limited to inserting the injector distally to the applied pressure.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art of record (Miller (1995, FASEB J., Vol. 9, pages 190-199; pg 198, column 1); Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, 1st ¶; pg 65, 1st ¶ under Conclusion section); Verma (Sept. 1997, Nature, Vol. 389, pages 239-242; entire article; pg 240, sentence bridging col. 2-3); Crystal (1995, Science, Vol. 270, page 404-410; pg 409).

The specification teaches injecting naked plasmid DNA encoding a protein operably linked to a promoter into an artery of an arm or leg of a monkey proximal to the injection site (pg 23, Example 1). Expression was obtained in skeletal muscle cells distal to the occlusion (pg 25-28, Example 3).

The specification does not enable delivering the polynucleotide to a blood vessel of a limb proximal to the applied pressure and delivering the polynucleotide to skeletal muscle cells of the limb distal to the applied pressure as broadly encompassed by claims 1 and 39. For example, the specification does not teach delivering DNA to a blood vessel in the upper leg with a cuff around the knee and obtaining delivery of the polynucleotide in muscle cells of the foot. In fact, the applied pressure would prevent delivery of the polynucleotide from the upper leg to the foot. It would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to deliver DNA to skeletal muscle distal to the applied pressure as broadly claimed. Therefore, claims 1 and 39 should be limited to injecting the polynucleotide distal to the site of applied pressure.

The specification does not enable one of skill to apply a tourniquet to the limb and inject a viral vector into a blood vessel of a limb distal to the tourniquet to obtain expression of a protein encoded by the vector in skeletal muscle cells (claim 3). Milas of record (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) taught injecting adenoviral particles to a femoral artery and vein occluded using a tourniquet passed under the inguinal ligament proximal to the site of injecting; however, the method did not result in expression in the muscle cells of limb (pg

2198, Fig. 1A and B, see legend and tourniquet in Fig. 1A; pg 2201, col. 2, 1st full ¶). Ye of record (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) also taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps did not result in expression in skeletal muscle. The specification taught delivering naked plasmid DNA but not viral DNA. The specification does not correlate the naked DNA in the examples with viral vectors. The specification does not discuss how to overcome the problems described by Milas. While the tourniquet described in the instant application is not passed under the inguinal ligament as taught by Milas, applicants have not correlated the obtained results of Milas with expected results obtained when the perfusion pump is not used and the tourniquet is not passed under the inguinal ligament. The difference between passing the tourniquet under the inguinal ligament and not passing the tourniquet under the inguinal ligament would be insignificant to one of skill in the art. It is not readily apparent that injecting an adenovirus using the method in claim 1 (applying a cuff, injecting the vector 5 minutes later and removing the cuff two minutes later) would cause protein expression because Milas taught an adenovirus perfusing through the leg for 13 minutes did not cause expression (pg 2199, col. 1, 2nd full ¶, last sentence).

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering naked DNA encoding a protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering naked DNA encoding a protein in the absence of a promoter.

The specification does not provide an enabled use for mere delivery of a polynucleotide to a skeletal muscle cell as claimed. For the delivery to have an enabled use, it must encode a protein that is expressed to detectable levels in the cell. Therefore, the claims should recite a final step of obtaining detectable levels of expression of the protein.

Applicants argue the specification enables more than delivering DNA encoding a marker protein operably linked to a promoter. Applicants argue a therapeutic gene is functionally equivalent to marker gene for the purposes of delivery using the method claimed. Applicants' argument is persuasive in part. Pg 9, lines 13-18, teach delivering gene products such as growth hormone, factor IX, etc to determine the amount of a secreted protein that a gene delivery procedure can produce and that "the reporter gene product can be assayed in a small amount of blood." Example 8, pg 31, teaches delivering plasmid encoding Factor IX to determine the amount of secreted protein in the sera and muscle. Therefore, the specification supports using therapeutic genes as marker proteins for delivery to skeletal muscle cells to determine the amount of therapeutic protein expressed in skeletal muscle cells. However, the genes described in the specification all require a nucleic acid sequence encoding a protein operably linked to a promoter. This is found in the Factor IX gene in example IX and the marker genes described throughout the examples. Therefore, the claims should be limited to a nucleic acid sequence encoding a protein operably linked to a promoter.

Applicants argue the polynucleotide does not have to encode a protein because it can encode an RNA molecule that is not translated into protein but has a cellular function itself. RNA not translated into protein would not be "expressed in the skeletal muscle cell" as claimed. The specification does not describe the polynucleotide recited in claims 1 or 39 as encompassing an RNA molecule that is not translated into protein "but has a cellular function itself." Therefore, the claims should be limited to DNA encoding a protein operably linked to a promoter.

Applicants' argue Miller, Deonarain, Verma and Crystal do not contemplate the process taught by applicants. Therefore, applicants conclude that progress has been made in the field of gene therapy by applicants, and Miller, Deonarain, Verma and Crystal cannot be given weight to support an argument that applicants' process cannot work. Applicants' argument is not persuasive. Applicants have not addressed the claims, which encompass inserting an injector into a limb proximal to the cuff and obtaining delivery of polynucleotides distal to the applied pressure. Applicants have not overcome the unpredictability of targeting polynucleotides to the desired tissue established by Miller, Deonarain, Verma and Crystal by teaching how to inject a limb with polynucleotides proximal to applied pressure and obtain delivery of the polynucleotides distal to the applied pressure.

III. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, new step c), the phrase "to occlude blood vessels in the limb" remains unclear for reasons of record. The phrase is an intended use and may not occur; therefore, it is unclear whether the blood vessel is occluded. In addition, the phrase does not clearly set for the blood vessel being occluded is the blood vessel into which the injector is inserted.

The phrase "impeding blood flow to the surface of skin" in claim 1, step b), is unclear. It is unclear if applicants are attempting to limit where the blood flow has been impeded (to the surface of the skin) or if applicants are attempting to limit where the device is applied (to the surface of the skin). The phrase does not clearly set forth that the device is applied to the skin

The metes and bounds of "sufficient pressure" required "to occlude blood flow to said limb" in claim 1, step c) is unclear. The specification and the art at the time of filing do not define the amount of pressure required to occlude blood flow as claimed.

The phrase "said occlusion" in claim 1, step d) lacks antecedent basis.

The rejection of claim 33 has been withdrawn because the claim has been canceled.

The rejection regarding the term "compressing" claims 34-36 has been withdrawn in view of the amendment.

The rejection regarding "applied over the skin" in claims 34-36 has been withdrawn in view of the amendment.

The metes and bounds of "cuff" remain unclear (claims 35, 36). The term does not have a defined meaning in the art. The specification defines "cuff" as a device for impeding blood flow in a blood vessel (page 5, line 13). While a sphygmomanometer cuff can be envisioned, and the specification states tourniquets are "cuff," other cuffs cannot be envisioned. Thus, the metes and bounds of devices encompassed by the term "cuff" cannot be determined. Does the cuff have to be applied to the outside of the mammal or is a string around the blood vessel a cuff? The definition provided in the specification is confusing. Is a cuff a "device for impeding blood flow through mammalian internal blood vessels" (line 13) or a "device applied to exterior to the mammal=s skin and touches the skin in a non-invasive manner" (line 14)? It cannot be determined which definition is to be applied. Therefore, the metes and bounds of the term cannot be determined. Applicants have not addressed this rejection.

The rejection of claim 39, step a), because it did not require the blood vessel was part of the mammal, has been withdrawn in view of the amendment.

The rejection of claim 39, step a), because it does not require the blood flow to be impeded within the mammal or within the blood vessel, has been withdrawn in view of the amendment.

Claim 39 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell. Applicants have not addressed this rejection.

Claim 39 step c as newly written is indefinite because it is unclear how "wherein function of the limb is not affected by inserting the injector, applying pressure to the vessel, and injecting the solution" is an active step.

Claim Rejections - 35 USC ' 102

IV. Claims 1, 3, 34-35 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) for reasons of record.

Milas taught administering adenoviral particles distally to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet applied to the skin of the rat that passed under the inguinal ligament. The claims require delivering the polynucleotides to skeletal muscles but do not require expression of the polynucleotides. Milas inherently obtains delivery of the polynucleotides to the skeletal muscles as claimed because the muscles showed small inflammatory cell infiltrates – an indication of the presence of foreign material (pg 2201, col. 2, 1st full ¶).

Applicants' argument regarding Fig. 3 on pg 2200 is noted. Fig. 3 describes the distribution of labeled red blood cells in the limb and not adenovirus. It is noted that the red blood cells leaked throughout the limb, which implies the adenovirus also leaked throughout the limb.

Applicants argue the method of Milas is different than the method used by applicants because Milas used perfusion to allow outflow of blood from the leg.

Applicants argue the claims "inherently results in no outflow". Applicants' arguments are not persuasive. The argument that the claims inherently result in no outflow is unfounded. The tourniquet described by Milas most definitely occludes inflow and outflow of blood to the leg. The claims encompass a tourniquet applied to the limb while a perfusion pump is applied. The claims do not exclude allowing outflow of blood using a perfusion pump while applying a tourniquet that occludes blood flow. The claims are not limited to occluding all outflow of blood from the limb.

Double Patenting

V. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 of copending Application No. 09/707117. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of delivering polynucleotides into limb blood vessels occluded using a device external to mammalian skin for delivery to skeletal muscle cells. Applicants' willingness to file a terminal disclaimer as necessary is acknowledged.

VI. Claims 1-3, 37 and 39 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,379,966. Although the conflicting claims are not identical, they are

not patentably distinct from each other because the method of '966 is an obvious species of claims 1-3, 37 and 39 in the instant application.

Applicants argue '966 did not teach applying a non-invasive cuff. Applicants' argument is not persuasive. The claims are not limited to applying a non-invasive cuff. '966 suggested applying pressure using clamps or other means (detailed description paragraph 82).

VII. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/917154. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share similar scope of inserting an injector into blood vessels of the limb, applying a device to the external skin and injecting a polynucleotide into the blood vessel.

Applicants argue '966 did not teach applying a non-invasive cuff. Applicants' argument is not persuasive. The claims are not limited to applying a non-invasive cuff. '966 suggested applying pressure using clamps or other means (detailed description paragraph 82).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER